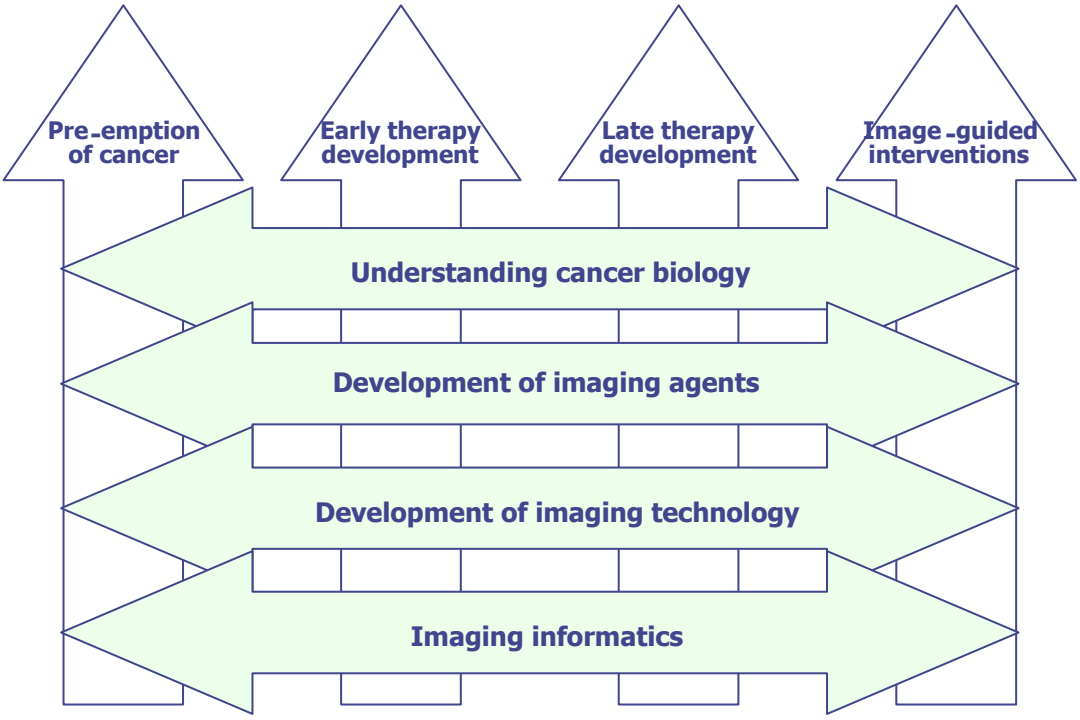
National Cancer Institute

I^2 Imaging Annual Report

FY 2005



CANCER IMAGING PROGRAM

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

I² Imaging 2005 Annual Report

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I2 Imaging Product Lines

Product Line	Line Manager	Board Liaison
Imaging for Cancer Prevention and Preemption	Gary Kelloff	Chris Berg
Imaging Tools for Early Therapy Development	Lalitha Shankar	Joe Tomaszewski
Imaging Tools for Late Therapy Development	Carl Jaffe	Jeff Abrams
Image-Guided Interventions (IGI) for Cancer	Gary Dorfman	Linda Weiss
Imaging for Understanding Cancer Biology	Anne Menkens	John Sogn
Imaging Agents for Oncology:	Jim Tatum	Peter Choyke
Imaging Technology for Oncology	Larry Clarke	Travis Earles/ Steven Taplin
Imaging Informatics for Oncology	Eliot Siegel	Ken Buetow

I² Imaging 2005 Annual Report

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June 2006

Letter to stakeholders

In FY 2005, *I² Imaging* set in motion a series of initiatives in eight interrelated areas, four of them related to cancer prevention, diagnosis, therapy, and evaluation of response to therapy and four of them charged with developing tools to support the first four.

During FY 2005, we added imaging components to therapy trials, created the National Cancer Image Archive (NCIA), established Image Response Assessment Teams in eight NCI-funded Cancer Centers, finished pre-clinical studies on two imaging agents and initiated synthesis chemistry for four more, established a lung cancer image database for software development in cooperation with industry in a public private partnership, and created an *in vivo* Imaging Workspace within the Cancer Bioinformatics Grid (caBIG). In the prevention, basic biology, and image-guided intervention areas, we have laid out paths forward.

These activities were significantly leveraged by inter-relating within the initiatives (e.g., by collecting images from ongoing therapy trials for the NCIA and planning early trials with new contrast agents); by integrating with on-going programs (e.g., by adding imaging evaluations to CTEP-funded trials); by professional society and academic cooperation (e.g., by encouraging the UPICT initiative); by industry funding (e.g., components of trials and contributions to the public-private-partnership for image databases).

In FY 2006, we expect to continue and expand these efforts, building on the progress we have made so far. We will support imaging in therapy trials, actively seek more trials for imaging evaluations, add images from three more trials to the archive, start an image-guided intervention trial, begin new probe syntheses and trials, and encourage the development of new software tools for evaluation of response to therapy.

I² Imaging is an experiment in applying a managed, directed business approach toward certain aspects of research and development. This approach leads to selected, predictable, specified deliverables that will in turn contribute in a fundamental way to attaining NCI's Goals. *I² Imaging's* products deliver important outcomes and capacities to our targeted end-users (researchers, providers of clinical care, patients, patient families, and the American public). Making available these validated imaging tools and image-guided interventions through support of development, optimization, and clinical trials will provide direct benefits to cancer patients and their families.

Daniel C. Sullivan
CEO, Chair, Board of Directors

Executive overview

I² Concept

Integration and Implementation (I^2) Teams
- **Bioinformatics**
- **Imaging**

Purpose
- **Create synergy, encourage coordination**
- **Focus initiatives to common goals**
- **Leverage investments**
- **Apply appropriate business strategies**

In 2004, the NCI Director and Senior Management Team created Integration and Implementation (I^2) Teams in the critical areas of Bioinformatics, Lung Cancer, and Imaging. These I^2 Teams were designed to: 1) create synergy among existing, related, but uncoordinated efforts within the NCI and, where appropriate, among multiple federal agencies, institutes, and centers; 2) focus initiatives that might have multiple alternative objectives on common high-priority objectives; 3) leverage pre-existing and/or new investments through the creation of such synergies and common objectives; and 4) apply business strategy principles including measurable short, intermediate, and long-term objectives and outcomes and measurable returns on investment. The I^2 Lung Team was subsequently converted to the Lung Cancer Program.

The I^2 Teams are intended to pursue transformational strategies. The I^2 Teams' business proposals are to implement critical activities that are either not included in the current NCI portfolio or are being pursued with a lack of coordination for which strategically applied incremental investment would significantly increase the impact.

I^2 *Imaging*

***I*^{2} *Imaging* pursues imaging projects that:**

- **Are not being done**
- **Are not being done in a coordinated way**
- **Are not being supported by peer-reviewed grants**
- **Are not being developed by the private sector**

***I*^{2} *Imaging* products are:**

- **Pathways to validate imaging tests as biomarkers**
- **Pathways to obtain application-specific FDA approval for ablative methods**
- **The infrastructure to accomplish those aims**

I^2 *Imaging* proposed a business plan along eight inter-related Product Lines. The overall strategy is to make highly leveraged critical investments designed to integrate activities across traditional NCI boundaries as well as with other federal agencies, institutes and centers, and external stakeholders such as academic investigators, professional societies, and various segments of industry.

Implementation of the strategic plan is focused on measurable short, intermediate, and longer-term outcomes that produce a substantial return on highly leveraged investments. This is the first Annual Report on progress and implementation of this integrated business plan and NCI investment in *I*^{2} *Imaging*.

This report will briefly summarize the Product Lines, their targets, their 2005 accomplishments, their plans, and how these fit the Vision of *I*^{2} *Imaging*.

Vision: "Imaging will have played a significant role in the elimination of death and suffering from Cancer."

I^2 *Imaging* Company-level Goals

- **Qualify imaging tests as biomarkers for therapy development**
- **Support development and delivery of image-guided interventions**
- **Make new imaging agents and technology available for research and clinical use**
- **Improve imaging informatics infrastructure**
- **Advance the role of imaging to detect and treat preneoplastic lesions**
- **Improve our understanding of communications between cancer cells and their environment**

The leveraging concept applied by *I*^{2} *Imaging*

***I*^{2} *Imaging* Investments Are Highly Leveraged.** The *I*^{2} *Imaging* business plan and budget request were created with full knowledge of the existing portfolio and evolving plans for investment in support of various activities including, for example, the *I*^{2} *Imaging* business plan itself, the other I^2 Teams' proposals, the CTWG (Clinical Trials Working Group) proposal and priorities, the Roadmap initiatives, the Interagency Oncology Task Force (IOTF), and non-NCI projects. Three broad types of leveraging are:

- Leverage internally among the I2 Imaging Product Lines and other I2 Teams
- Leverage other existing investments within the NCI
- Leverage ongoing initiatives funded external to the NCI

Examples of leverage internally among the *I² Imaging* Product Lines and the other I² Teams include:

- **Creating NCIA in the Imaging Informatics Product Line as a support i**nfrastructure for clinical trials in the other Product Lines and using it in the in vivo Imaging Workspace in caBIG
- Performing pre-clinical and feasibility studies in the Imaging Agent Product Line on novel imaging agents and evaluating them for biomarkers in the Early and Late Therapy Product Lines
- Interrelating the Cancer Prevention And Pre-Emption Product Line with the Image-Guided Intervention Product line in the treatment of early cancers and pre-cancers
- Coordinating the I2 Imaging Informatics Product Line with caBIG and the evolving I2 Bioinformatics Plan

Examples of leverage of other existing investments within the NCI include:

- Creating and integrating Lung Cancer-specific IRATs within the Lung Cancer Program
- Creating software within the I2 Imaging Informatics Product Line to support the ACRIN NLST bio-repository, partially funded by the Lung Cancer Program
- Adding imaging correlative studies to clinical trials funded through CTEP
- Funding collaboration between the NCI funded Cooperative Group ACRIN and various NCI-funded therapy Cooperative Groups
- Implementing Imaging Response Assessment Teams (IRATs) within NCI-funded Cancer Centers
- Using National Cancer Imaging Archive (NCIA) to support the already funded LIDC, RIDER, and IDRI imaging database projects
- Creating the in vivo Imaging Workspace within caBIG to bring imaging expertise to the other Workspaces
- Integrating I2 Imaging with the recently created intramural imaging program in the CCR and the evolving animal imaging facility at Frederick
- Integrating development of imaging agents with the NCI Nanocharacterization Laboratory

Examples of leverage with initiatives funded external to the NCI include:

- Engaging industry and professional organizations in the caBIG in vivo Imaging Workspace
- Involving caBIG in vivo Imaging Workspace with the DICOM, HL7, and RADLEX efforts (RSNA)
- Integrating DICOM fields, RADLEX terms, and the ACRIN lexicon into the Vocabulary Services/Common Data Elements (EVS/CDE) and caDSR (cancer Data Standards Repository) into the caBIG in vivo Imaging Workspace in cooperation with experts from DICOM, RADLEX, and ACRIN,
- Forging collaboration among NCI, FDA, CMS, academia, and industry in IGI trials
- Developing software within the Imaging Informatics Product Line to support the Image Database Resource Initiative (IDRI), which is partially funded by Industry in a public-private partnership (PPP)

Products fully funded by *I*^{2} *Imaging*

Product Line	Product
Imaging for Cancer Prevention and Preemption	Planning for prevention and preemption Workshop
Imaging Tools for Early Therapy Development	Planning for two-site trial of FLT in NSCLC; Support for Fellow at Clinical Center
Imaging Tools for Late Therapy Development	Eight Image Response Assessment Teams in the Cancer Centers
Image-Guided Interventions (IGI) for Cancer	Workshop held to plan the product line
Imaging for Understanding Cancer Biology	Planning for Workshop: Imaging the Tumor and Its Microenvironment
Imaging Agents for Oncology	Pre-clinical studies on ^{64}Cu-ATSM Pre-clinical studies on ^{18}F-Galacto-RGD Synthesis Chemistry on ^{18}F-fluoromisonidazole Synthesis Chemistry on ^{111}In-Hherceptin Synthesis Chemistry on ^{18}F-fluoroestradiol Contract for ^{18}F-fluoro-L-thymidine supply
Imaging Technology for Oncology	Extension of LIDC database
Imaging Informatics for Oncology	National Cancer Image Archive *In vivo* Imaging Workspace

Products with leveraged funding

Product Line	Product	Source of leveraged funding
Imaging Tools for Early Therapy Development	Added imaging biomarker studies to two trials	CTEP primary support of Trial; *I2 Imaging* funded biomarker portion
Imaging Tools for Late Therapy Development	Collection of pre and post treatment PET-CT	CTEP primary support of Trial; *I2 Imaging* funded image archive portion
	UPICT initiative	American College of Radiology
	PET-CT & CT Images for Archive	Novartis funded trials, *I2 Imaging* funded image transfer
	Serial CTs in carcinoid therapy trial	Genentech will fund in FY 2006 through CTEP
Image-Guided Interventions (IGI) for Cancer	Added PET imaging to a trial of radiofrequency ablation of liver tumors	CTEP primary support of trial with some industry support; *I2 Imaging* funded PET acquisition
Imaging Agents for Oncology	Precursors for CuATSM and In-Herceptin	DTP funding precursor acquisition
Imaging Technology for Oncology	Image Database Research Initiative	Imaging device industry, through an FNIH PPP
Imaging Informatics for Oncology	Imaging Workspace	caBIG

Vertical Product Lines: Achievements and Plans

Imaging for Cancer Prevention and Preemption

Vision: By 2015, imaging will play a significant role in the prevention and preemption of cancer.

Goal: Use imaging to define the cancer risk and precancer burden in individuals and aid, augment, and monitor therapies for treatment and prevention of cancer and precancer.

- **Product line leader: Gary Kelloff**
- **Product line consultants:** Larry Clarke, Gary Dorfman, DCP staff
- **Milestones achieved for 2005:**
  - Planned workshop
  - Engaged Dr. Denise Aberle as an IPA
- **Milestones for 2006:**
  - Hold workshop
  - Research plan with goals
  - State of the science publication

Achievements funded in 2005

The opportunities for imaging science to contribute to the detection, diagnosis, therapy, and evaluation of therapy in individuals with precancer are exciting. We will provide a research plan for imaging science to support cancer prevention and preemption and, to that end, have planned a comprehensive workshop in July 2006 with imaging scientists and other experts actively working in the field of cancer prevention and preemption. Expert participants have been identified to participate in this workshop.

Dr. Denise Aberle was engaged as an IPA to assist this product line. Dr. Aberle is a Professor of Radiological Sciences and Director of Thoracic Imaging at UCLA Medical Center. She is currently leading the NLST (National Lung Screening Trial), a multi-center national endeavor.

Future Plans

The 2006 workshop will identify the human populations at risk for cancer from epidemiologic, pathologic, genetic and molecular biology data and will consider the application of imaging modalities to evaluate these risks. Specifically, we will discuss precancer and early cancer in esophagus (Barrett's), bladder, breast,

prostate, lung, colon, pancreas, ovary, head & neck, cervix and skin. Among the topics to be discussed:

- Relative and absolute risk for developing cancer over a defined time interval
- Clinical and preclinical data from all imaging modalities identifying early cancer, precancer lesions or predysplastic molecular lesions associated with cancer risk
- Image-guided intervention (IGI) methods for intervention in precancer and early cancer in clinical and preclinical settings
- Complementing or replacing drug intervention or surgery with IGI in patients with precancer lesions

Sessions on each target organ will feature a keynote speaker, who will provide a comprehensive overview with the objective of identifying precancer and early cancer settings where imaging would improve risk detection or treatment. The keynote speaker will be followed by several speakers reviewing the use of imaging in the clinical setting or specific imaging applications for use in detecting or treating the precancer or early cancer.

Roundtable discussions following each session will include experts from industry, academia, NCI and FDA. The feasibility of developing imaging-based biomarkers to evaluate risk and guide intervention in the target organs and the development effort needed to qualify them for clinical use will be considered. The participants will consider the components of a research plan to develop high priority imaging-based biomarkers.

A research plan with an overarching work plan with multiple specific complementary projects will be the primary outcome from the workshop. The plan will be integrated and prioritized and will include one, three, five, and ten year objectives with suggested budget, milestones, ROI, and mechanisms for implementation. It is expected that the research plan will suggest FY2007 funding for 2–4 targeted supplements for diagnostic imaging and 1–3 supplements for IGI.

A second outcome of the workshop will be a state-of-the-science overview of imaging in cancer prevention and preemption (treatment of precancer and early disease), including the perspectives of the scientists participating in the workshop on opportunities and research and development work needed to advance the field. This review will be prepared for publication in a peer-reviewed oncology journal and will provide background to attract scientists to the field.

Imaging Tools for Early Therapy Development

Vision: By 2015, imaging will play a significant role in making "go/no-go" decisions for early therapy development.

Goal: Use imaging methods to decrease the time and cost involved in early oncologic drug development.

- **Product line leader: Lalitha Shankar**
- **Product line consultants:** Peter Choyke, Joe Covey, Barbara Croft, Melinda Hollingshead, Paula Jacobs, Gary Kelloff, Anne Menkens, Tony Murgo, Jim Tatum
- **Milestones achieved for 2005**:
  - Added design elements and funding support through ACRIN to two planned CTEP trials to perform blinded central RECIST evaluations and DCE-MRI in renal cell carcinoma and FDG-PET in metastatic melanoma
  - Planned two-site trial of FLT in NSCLC
  - Provided support for Fellow at the Clinical Center
- **Milestones for 2006:**
  - Initiate planned trials
  - Develop protocol and initiate trial of hypoxic indicator 18F-MISO (see Imaging Agents For Oncology section)

Therapeutic drug development usually takes more than a decade from discovery to approval and is very expensive. Many drugs fail late in the process of development after significant investments of time and money, raising the development costs of all drugs. Imaging information can assist in critical go/no-go decisions at several points in the preclinical and the Phase I-III clinical development, speeding drug development and lowering drug development costs.

Evaluation of potential biomarkers is a major NCI priority, as evidenced by the Interagency Oncology Task Force (IOTF) and the Oncology Biomarker Qualification Initiative (OBQI). Activities of this product line and the Late Therapy Development Product Line are tightly integrated with IOTF and OBQI.

This product line is particularly synergistic and integrated with the Imaging Agents for Oncology Product Line and evaluates the role of imaging in early phase clinical therapy trials for the evaluation of response of solid tumors to experimental therapeutic agents by use of:

- Serial anatomic (CT, MR) imaging for evaluating solid tumor response to therapy using RECIST criteria
- Established functional imaging tools (FDG-PET, DCE-MRI) to evaluate the efficacy of therapeutic agents

- New molecular imaging agents targeted to biological processes such as hypoxia, proliferation, and angiogenesis to evaluate the efficacy of therapeutic agents
- Receptor-targeted molecular imaging agents such as fluoroestradiol (FES) and fluorodihydrotestosterone (FDHT) to evaluate the efficacy of therapeutic agents
- Pharmacokinetic and pharmacodynamic evaluations in clinical trials, for example, by labeling the therapeutic compound that is being evaluated with a radioactive or magnetic moiety

The majority of clinical trials evaluate changes in tumor size using RECIST, but very few do so in a standardized fashion, or incorporate independent blinded image evaluations. Currently, the use of imaging as a biomarker to evaluate response, disease-free survival (DFS), or progression-free-survival (PFS) is limited. Overall survival (OS) continues to be the primary endpoint for assessment of therapeutic response.

Growing evidence in the scientific literature suggests that FDG-PET and DCE-MRI may be significantly more sensitive in predicting therapeutic response than anatomic imaging, such as CT and MRI. The Cancer Imaging Program (CIP) held workshops in November 2004 (DCE-MRI) and January 2005 (FDG-PET) focusing on each of these functional imaging modalities to develop a consensus for standardized image acquisition and interpretation criteria. Demonstration projects have been planned for RECIST, and for each of the functional modalities, compared with RECIST, in Phase II evaluations of combinations of molecularly targeted therapies. These protocols will use acquisition and interpretation criteria for FDG-PET and DCE-MRI based on the results of the CIP workshops to evaluate therapeutic response.

Achievements funded in 2005

Evaluation of an imaging agent for assessing the proliferation status of a tumor. The evaluation of response to therapy in non-small cell lung cancer by ^{18}F-fluoro-L-thymidine (FLT-PET), which assesses tumor proliferation, will be compared to FDG-PET, which assesses metabolism. This study will be done at Johns Hopkins University and Virginia Commonwealth University. The protocol is partly developed and funds have been committed for this project.

CCR Fellow at NIH Clinical Center. Financial support was provided for the appointment of a CCR Fellow to assist Peter Choyke in the Molecular Imaging Program, as well as the Cancer Imaging Program to aid in implementing and conducting of Phase 0 and Phase I/II trials.

Achievements leveraged in 2005

Evaluation of Blinded RECIST Evaluation and of DCE-MRI in the Assessment of Therapeutic Response. The value of blinded RECIST evaluations and of DCE-MRI (dynamic contrast enhanced MRI) in the evaluation of response to therapy will

be studied in advanced renal cell carcinoma (E2804 - A Randomized Phase II Study of VEGF, Raf kinase, mTOR, and EGF-R Targeted Combination Therapy in Advanced Renal Cell Carcinoma (Bevacizumab, Sorafenib, CCI-779, and Erlotinib).

I² Imaging will fund the central collection of CT and MRI scans and blinded image evaluations for RECIST measurements and an evaluation the role of DCE-MRI as a measure of the response of renal cell carcinoma to therapy. The goals of the added imaging aspects are to evaluate the blinded application of RECIST criteria, determine the feasibility of performing DCE-MRI in a multicenter study, and determine if DCE-MRI can aid in evaluating response to therapy. This protocol is expected to open in the summer of 2006, with the majority of the funding from CTEP. *I² Imaging* provided a funding supplement to ACRIN to manage the imaging aspect of this trial.

This study is indicative of the synergy that can be achieved by adding imaging aspects to therapeutic trials, and of the leveraging that is possible when *I² Imaging* is involved in the early discussions of therapy trials.

Evaluation of the Role of FDG-PET in the Assessment of Therapeutic Response: The value of FDG-PET to evaluate response to therapy in malignant melanoma is being studied in a Phase II setting. The protocol has been developed as a SWOG-ACRIN study, S0438, "Randomized Phase II Trial of Sorafenib (NSC-724772, BAY 43-9006) plus Temsirolimus (NSC-683864, CCI-779) or Sorafenib plus Tipifarnib (NSC-702818, R115777) in Untreated Metastatic Melanoma". This protocol has successfully completed CTEP review and is undergoing local Institutional Review Board (IRB) review at the participating institutions. The trial is expected to open in the spring of 2006 with the majority of the funding from CTEP. *I² Imaging* provided a funding supplement to ACRIN to manage the imaging aspect of this trial.

Future Plans

Initiate planned trials.

- FLT vs. FDG in lung cancer therapy response
- RECIST and DCE-MRI in renal cell carcinoma therapy response
- FDG-PET in melanoma

FMISO. Protocol development and initiation for trial of hypoxic indicator FMISO (see Imaging Agents for Oncology section)

Monitor early therapeutic trial proposals. Opportunities to add imaging evaluations to early therapy trials within CTEP will be evaluated on an on-going basis. We will actively seek information about industrial trials as well, and encourage addition of imaging evaluations to them.

Imaging Tools for Late Therapy Development

Vision: By 2015, imaging tests or methods will serve as surrogate markers of therapy response for late-phase clinical trials.

Goals: Develop a pathway and perform demonstration projects to test that pathway to qualify anatomic, dynamic, and molecular imaging methods as reliable surrogate markers for therapy response.

- **Product line leader: Carl Jaffe**
- **Product line consultants:** Barbara Galen, Gary Kelloff, Paula Jacobs, Lalitha Shankar, Eliot Siegel
- **Milestones achieved for 2005:**
  - Added PET-CT for response to therapy in head and neck cancer
  - Funded IRAT program
  - Funded image archive workshop
  - Stimulated formation of UPICT initiative
- **Milestones for 2006:**
  - Open trial of FDG-PET for response to therapy in lung cancer
  - Hold archive workshop
  - Begin image transfer from RTOG 0522
  - Begin image transfer from Novartis
  - Demonstrate transfer of image set from ISpy trial

The objective of this product line is to facilitate the validation of imaging as a biomarker or surrogate for clinical outcomes. As with the Early Therapy Development Product Line, the activities of the Late Therapy Development Product Line are closely integrated with IOTF and OBQI. Activities include assembling clinical images into digital data sets combined with matching clinical data and outcomes from Phase III therapy trials. Achievements in this product line were significantly leveraged with funds from outside of I^2 *Imaging*.

Achievements funded in 2005

FDG-PET in the Evaluation of Therapy for Head and Neck Cancer. Pre- and post-therapeutic PET-CT images will be acquired from a large portion of the 503 patients in a recently initiated therapy trial (RTOG-0522, Randomized Phase III Trial of RT and cisplatin vs. RT, cisplatin and cetuximab followed by surgery for selected patients for stage 3-4 head and neck carcinomas). An agreement was reached between RTOG (Radiation Therapy Oncology Group) and ACRIN (American College of Radiology Imaging Network) to collect imaging data. The trial opened to accrual in November 2005. ACRIN is preparing and training the accruing sites to transfer the PET image and raw data (+/- CT) first to ACRIN's image repository, and then to NCIA (National Cancer Image Archive) with an approximately 300 cases expected. Case accrual is already underway and uniform image acquisition is being

employed. RTOG has agreed to transfer the post-therapy surgical results and the Advanced Technology Consortium (ATC) of radiotherapy has agreed to transfer and integrate the RT planning and RT/CT data on these patients to the same NCI image archive. Thus, the archive will have a large number of cases with baseline and response images, radiotherapy data, and surgical information that can be used to validate quantitative measures of response as well as provide a resource for the design of computer-aided detection and diagnosis tools. I^2 *Imaging* funding was committed to ACRIN for the imaging aspects of this trial in 2005.

NCI IRAT (Image Response Assessment Team) Supplemental Awards. IRAT Supplement Awards were administratively funded in the fall of 2005 to eight imaging teams in Cancer Centers to advance the role of imaging in assessment of response to therapy. In the 2005 NCI-sponsored RFA, 31 Cancer Center respondents provided cohesive plans to enhance involvement in quantitative analysis, interpretation, and integration of imaging data in response to therapy trials and eight of them were funded. Their plans also included a means for regular dissemination and communication of these methods with IRATs at other institutions in a process managed by the American Association of Cancer Institutes (AACI). The long-term objective of these awards was to increase clinical collaboration between imaging scientists and oncologic investigators at Cancer Centers. The teams will identify new oncologic imaging research opportunities in clinical trials that warrant multi-center clinical investigations and integrate imaging data as potential biomarkers or candidate surrogate markers in clinical therapeutic trials. The IRAT supplements will strengthen the imaging team and its engagement in oncologic trials but will not finance the cost of imaging procedures in specific trials or purchase imaging equipment. *I2 Imaging* funded eight administrative supplement awards in FY 2005. FY 2006 and FY 2007 funding will continue through the Cancer Center program.

Archive Workshop. Funding commitment was made in 2005 for a workshop planned for spring 2006 to bring together seven Cooperative Groups that have imaging archives, the American College of Radiology Imaging Network (ACRIN), Quality Assurance Review Center (QARC), Children's Oncology Group (COG), Pediatric Brain Tumor Consortium (PBTC), Cancer and Leukemia Group B (CALGB) and the Advanced Technology Consortium (ATC). The purpose of the workshop is to discuss how their image archives can become interoperable and compatible with NCI caBIG to provide a wider database for image-connected-metadata validation of biomarker surrogacy.

Leveraged activities not requiring I^2 *Imaging* funding

CT evaluation of response to therapy in patients with carcinoid. A trial testing differing therapies for carcinoid (SWOG S0518, Phase III, Prospective, Randomized Comparison of Depot Octreotide Plus Interferon Alpha with Depot Octreotide plus Bevacizumab in Advanced, Poor Prognosis Carcinoid Patients) will commence accrual in early 2006, enrolling approximately 280 imaging-evaluable patients over a 43-month period. For one endpoint, progression-free survival, imaging plays a critical role. Each patient will have six CTs (a total of

1848 CT scans for the 280 subjects) and an optional diagnostic SPECT octreotide scan. The images will be centrally collected and read by ACRIN and transferred to NCI on a yearly basis for archiving. The archive will be made available to the community for secondary analyses when the trial is completed.

This trial was planned during FY 2005. Funding is expected to be provided beginning in FY 2006 by Genentech through CTEP.

ACR UPICT (Uniform Protocols for Imaging in Clinical Trials) Initiative. The American College of Radiology (ACR) and NCI Cancer Imaging Program have been working together to strengthen imaging's contributions as key response data in clinical trials. Imaging's lack of reproducibility as quantitative data, often caused by a lack of uniformity in protocols across the many sites required for patient accrual, has hindered full acceptance of imaging data. Consensus on imaging protocols used in multi-site clinical trials, particularly for the most widely used imaging in oncology such as CT, MRI, DCE-MRI and FDG-PET, would greatly accelerate the acceptability of imaging as a measure of clinical response. The ACR, with NCI's encouragement, convened a broad spectrum of participants in September 2005 and again in January 2006 that included diagnostic radiologists, radiation oncologists, medical physicists, clinical trial experts, government agency representatives and industry representatives to form an open process for developing consensus on sets of recommended imaging protocols (http://upict.acr.org) in clinical trials. The effort recognized that existing installed imaging technology is varied and research-imaging procedures must reasonably be accommodated in the context of usual care. It also acknowledged that there are rapid advances in technology and so the process proposed will incorporate some scheme for change management while providing periods of stability through predictable, pre-announced version control. The first set of CT protocols are planned to be disseminated by late 2006. No funding by I^2 *Imaging* was necessary.

Image data for Archive. Non-funded image/metadata commitments for other phase III trial images to be transferred into the NCIA have been made in 2005 for trials sponsored by pharmaceutical companies. A prime contribution will be CT and PET-CT images from Novartis therapy trials in lung cancer. I^2 *Imaging* will fund only the cost of image transfer.

Future Plans

Validation of FDG-PET for response to therapy in NSCLC. This study is designed to validate treatment monitoring with FDG-PET in patients with advanced lung cancer using the standardized uptake value (SUV) to provide an early predictor of the effectiveness of therapy. Patients with newly diagnosed or recurrent non-small cell lung cancer (NSCLC) scheduled to undergo palliative chemotherapy with a standard regimen will have PET-CT scans before and after the first and second chemotherapy cycles. The primary endpoint of this study is the prediction of overall patient survival by monitoring the metabolic response (defined as ≥ 20% decrease in the SUV) of the tumor relative to baseline of the tumor during the first chemotherapy cycle. Metabolic response will also be compared to RECIST and the

test-retest reproducibility of standardized uptake values (SUVs) measured by PET-CT systems will be evaluated. This trial is being planned in 2006, and may be initiated by the end of FY 2006 and will be funded through ACRIN. This trial is part of an NIH GPRA goal.

Hold archive workshop. See description on page 14.

Begin image transfer from head and neck trial. Some image sets should be available by late spring 2006 to test the transfer. Once the process is established, image sets will be transferred on a regular basis.

Finalize the image transfer process from Novartis. A contract will be finalized and image transfer should begin in 2006 and continue for two years.

***Demonstrate transfer of image set from I-Spy trial*.** The I-SPY Trial (Investigation of Serial Studies to Predict your Therapeutic Response with Imaging and Molecular Analysis) is a joint CALGB and ACRIN trial testing the hypothesis that molecular and imaging markers will predict response to therapy and determine outcome. The following data elements are in a common database: molecular profiles (DNA copy number, expression arrays), specific therapeutic targets (ER, PR, erbB2, EGFR, Topo 2), proteomic profiles (serum, tissue phosphoproteins, and cell lysate arrays), and volumetric response (pre- and post-cycle MRI imaging of the breast). The informatics project has these goals: to collect and share biomedical research study results with the community; to integrate biomedical research study results in support of translational research; to capture the biomarkers that predict response to therapy throughout the course of the cancer treatment cycle; to facilitate cross-platform validation of markers; and to accelerate our ability to find robust biomarkers.

Initially, MRI images were shared in the database only as jpeg images. Adding the DICOM MRI images to the caBIG I-SPY database will encourage use of more sophisticated volumetric quantitative methods of tumor response. This will aid in determining the value of MRI to predict disease-free-survival at 3 years, to compare MRI change to pathologic response, to refine definition of tumor types by pattern of tumor in the breast, and to associate molecular markers with specific MR imaging patterns.

Image-Guided Interventions (IGI) for Cancer

Vision: By 2015, image-guided interventions (IGIs) will play a major role in eliminating the death and suffering due to cancer.

Goals: Develop the infrastructure, procedures, and processes necessary to obtain application-specific FDA approval of IGI devices and conduct demonstration projects to test this pathway.

- **Product line leader: Gary Dorfman**
- **Product line consultants:** Larry Clarke, Barbara Croft, Jim Deye, Keyvan Farahani, Barbara Galen, Carl Jaffe, Gary Kelloff, Meg Mooney, Scott Saxman, Lalitha Shankar, Brad Wood
- **Milestones achieved for 2005:**
  - Workshop held
  - Imaging added to IGI therapy trial.
- **Milestones for 2006:** Initiate trials using microwave and cryoablation for therapy

The long-term goal for the Image-Guided Intervention (IGI) Product Line is to make IGI oncologic therapies widely available to patients. IGI therapies are device-based, minimally or non-invasive therapies that utilize real-time, intraprocedural imaging and/or sensing for guidance, monitoring, and procedural endpoint determination. To accomplish this goal, IGI therapies must be developed, optimized, standardized, validated, approved by FDA, reimbursed and made widely available.

Potential disease-specific clinical utilities for IGI therapies are:

- Primary or secondary palliation to treat signs and symptoms and improve progression-free-survival
- Adjunctive therapy to improve the outcome of other therapies or to bridge the time to definitive therapy
- Cure in patients with localized disease or precancerous lesions

The NCI currently supports the development and investigation of cancer pharmacotherapies to establish their clinical utility, but does not have an equivalent process for investigation of device-based, image-guided oncologic therapies. Furthermore, the current regulatory environment does not encourage disease-specific indications for device-based, image-guided therapies, so little hard evidence is available to guide the use of such treatments.

This product line will establish processes and infrastructure to achieve for device-based therapies what the NCI has accomplished so well for pharmacotherapies, while accommodating the critical differences between drugs and devices in their use, regulatory and reimbursement policies, industrial base, and clinical trial design constraints.

The long experience of the NCI in the development and dissemination of pharmacotherapies can help avoid failed strategies, choose among alternative implementation strategies on the basis of previous experience, and re-purpose existing processes and infrastructure whenever possible (i.e., leveraging existing investments).

Achievements funded in 2005

Workshop. A workshop was completed in October 2005 to validate the IGI product line's goals and vision and to determine a detailed plan based on input from FDA, CMS, industry, academia, and NCI. The workshop achieved the desired objectives of a plan that is being implemented during FY 2006 and/or proposed for FYs 2007 – 10.

Achievements leveraged in 2005

Clinical Trial of Radiofrequency Ablation in Lung Cancer Patients. This phase II trial is to determine the effectiveness of CT-guided radiofrequency ablation (RFA) in treating patients with stage I non-small cell lung cancer who are not able to undergo resection (ACOSOG Z4033: Radiofrequency Ablation in Treating Patients With Stage I Non-Small Cell Lung Cancer). The patient will also have a post-RFA FDG-PET scan to assess the treatment, and clinical follow-up for 2 years post-treatment. I^2 *Imaging* provided funding for the post-therapy PET scan, the transmission of images to ACRIN, and the archival of images and clinical data within the NCIA. The remainder of the trial is being funded by ACOSOG through CTEP and Radionics (Valley Lab division of Tyco Healthcare). This trial will be activated shortly.

Leveraged Activities. The IGI Product Line leverages pre-existing investments and collaborations.

The infrastructure for IGI clinical trials will reuse existing NCI investments such as

- Legal documents (e.g., CRADA, CTA, CSA)
- LOI, concept and protocol review mechanisms (e.g., disease-specific strategy groups and task forces, CRM, PRC)
- Clinical trials groups (e.g., Cooperative Groups, CCOPs)
- Data management infrastructure (e.g., CTSU).

Other I^2 *Imaging* investments will be used by this Product Line such as the image archive (NCIA) and imaging tools to support early and late phase clinical trials.

The early phase investigations will likely be created through collaboration with Cancer Centers and utilize the CTSU for data management and support, thus building on existing resources and creating new collaborations.

The clinical trials will be co-funded by industry collaborators, reducing the cost of the trials to the NCI. These trials will also encourage new collaborations by

integrating clinical scientists specializing in IGI therapies within existing research structures such as the Cooperative Groups, Cancer Centers, and SPOREs.

Future Plans

Based on the 2005 workshop, the following objectives for subsequent years have been identified:

- Establish a forum for the NCI, FDA, and CMS to prioritize important research questions that might be answered by federally funded early or late phase clinical trials. (FY 2006 initiation with subsequent year continuation)
- Create a process by which clinical trials of mutual interest to NCI and FDA can achieve "conjoint" review and approval (FY 2006)
- Bring two clinical trials through whatever process is established during 2006 resulting in NCI and FDA approved protocols (FY 2006-7)
- Propose additional clinical trials to use this process during the FY 2007 and subsequent years (FY 2007 with continuation through 2010)
- Engage a cadre of investigators for the conduct of early phase clinical trials of image-guided, device-based oncologic therapies (FY 2006 proposal for FY 2007 implementation and subsequent year continuation)
- Establish a mechanism for the issuance of solicitations and subsequent review of LOIs/Concepts leading to clinical trials (FY 2007).

Horizontal Product Lines: Achievements and Plans

Imaging for Understanding Cancer Biology

Vision: By 2015, high-resolution *in vivo* imaging in molecular and cellular biology will be instrumental in defining fundamental genetic and biological processes involved in tumorigenesis, metastasis and complex interdependencies between tumor cells and their microenvironment.

Goal: Make widely available the *in vivo* molecular imaging tools necessary to noninvasively and quantitatively interrogate the cancer cell, its tumor microenvironment, and its response to therapy.

- **Product line leader: Anne Menkens**
- **Product line consultants:** Barbara Croft, Cheryl Marks, Suresh Mohla
- **Milestones achieved for 2005:**
  - Engaged Dr. Bonnie Sloan as an IPA
  - Planned Workshop on Imaging the Tumor and Its Microenvironment for 2006
  - Planned Cancer Imaging Camp for 2007
- **Milestones for 2006:**
  - Hold Imaging the Tumor and Its Microenvironment Workshop,
  - Finalize plans for Cancer Imaging Camp

This Horizontal Line is at the discovery end of the "discovery-development-delivery" continuum and is critically dependent on the productive interaction of basic cancer biologists with cancer imaging scientists. Facilitation of these critical interactions, both within the NCI and with outside investigators, was initiated during the first year of the I^2 *Imaging* Project.

Achievements funded in 2005

IPA Engaged. Dr. Bonnie Sloane, an expert in the role of proteases in the development and progression of cancer, was engaged through I^2 *Imaging* as an IPA. As a grantee funded through the Division of Cancer Biology, Dr. Sloane has had a long working relationship with NCI and has greatly facilitated the establishment of the I^2 *Imaging* - Cancer Biology Team.

Future Plans

Workshop: Imaging the Tumor and Its Microenvironment- to be held June 8-10, 2006. The goal of this Workshop is to formulate a plan to encourage investigators to use imaging in studies of the tumor microenvironment. Participants will identify mechanisms that will facilitate the use of imaging, including imaging as a tool to assess the efficacy of therapies targeting the tumor and its microenvironment. Lung cancer, a major priority for the NCI, will be an important area of focus for this Workshop. Since the imaging of lung cancer is not as advanced as imaging of some other cancers, imaging the microenvironment of

breast cancer will be used as a paradigm for studies on lung cancer. This Workshop will provide the *I² Imaging* - Cancer Biology Team with the input necessary from the community to formulate an integrated, prioritized action plan to include 1-, 3-, 5- and 10-year objectives with suggested budget, milestones, ROI, and mechanisms for implementation.

Cancer Imaging Camp - to be held June 24-29, 2007. To apply imaging tools more effectively into basic cancer biology research, a clear need for more in-depth training for cancer biologists was identified by the *I² Imaging* - Cancer Biology Team. As a major activity of this Product Line, NCI will sponsor a weeklong Cancer Imaging Camp at Duke University. The "Camp" will offer both didactic lectures and hands-on laboratory sessions geared specifically towards young cancer biologists. Experts from the imaging community will present the basics of all *in vivo* imaging modalities. Although hands-on access to equipment will only allow 16 students to attend the Camp in person, the didactic lectures will be made available through webcast to the entire cancer community. These educational sessions will empower a new generation of scientists with the knowledge to discover and assess novel cancer pathways and targets that will be clinically relevant.

Imaging Agents for Oncology

Vision: By 2015, high impact imaging agents (including nanoconstructs) will be a pivotal resource for oncology research and clinical care.

Goal: Make widely available a portfolio of imaging probes that will be critical to elucidating tumor biology, accelerating drug development, optimizing detection, and directing therapy for cancer.

- **Product line leader: Jim Tatum**
- **Product line consultants:** Joe Covey, Barbara Croft , Paula Jacobs, Gary Kelloff, Tony Murgo, Lalitha Shankar
- **Milestones achieved for 2005:**
  - ^{64}Cu-ATSM pre-clinical completed
  - ^{18}F-FMISO synthesis implemented
  - ^{18}F-Galacto-RGD pre-clinical completed
  - ^{111}In-Herceptin project begun
  - ^{11}C-SN38 project planned
  - ^{18}F-FES synthesis being developed
  - ^{18}F-FLT supply contract planned
- **Milestones for 2006:**
  - Contract for ^{18}F-FLT supply
  - Contract for ^{11}C-SN-38 synthesis
  - IND for ^{18}F-FMISO
  - IND for ^{18}F-FES
  - Contract for ^{18}F-Galacto-RGD synthesis
  - eIND and Phase 0 protocol for ^{18}F-Galacto-RGD
  - Contract for ^{111}In-Herceptin precursor

Imaging probes will be developed in response to critical needs identified by I^2 *Imaging* product lines, DCTD and CCR programs, NCI initiatives, and cancer research and clinical provider community. This product line does not support the discovery of new imaging entities but may include the labeling of an existing entity or optimization of an imaging construct requiring probe alterations. In addition to the routine IND-directed studies such as pharmacology, safety, and toxicology, imaging agents require considerable resources and time to perform multi-level validation, imaging feasibility, and optimization studies. This product line is particularly synergistic and integrated with the Imaging Tools for Early Therapy Development Product Line.

Achievements funded in 2005

^{18}F-MISO (^{18}F-Fluoromisonidazole) is a PET probe for *in vivo* evaluation of hypoxia, a high interest micro-environmental target known to impact tumor biology and subsequent treatment efficacy. FMISO has been extensively evaluated in humans and there is an investigator-sponsored IND for the manual production of the agent. For this probe to be useful in widespread clinical applications a method of automated synthesis or commercial availability is essential. The investigators holding the IND were contracted to develop an automated synthesis procedure appropriate for a multi-site clinical trial and prepare the documents required for an IND. These documents include synthesis and testing SOPs, specific sections of the IND, and an IND-enabling protocol. The required precursor for trials was obtained by subcontract to a commercial supplier.

Milestones:

- Automation and documentation completed.
- IND-enabling protocol drafted
- IND preparation in progress

^{18}F-FES (^{18}F-16-α-fluoroestradiol) is a PET imaging probe for estrogen receptor expression. FES has been extensively used in humans and there is an investigator-sponsored IND for the manual production of the agent. For this probe to be useful in widespread clinical applications a method of automated synthesis or commercial availability is essential. The investigators holding the IND were contracted to develop an automated synthesis procedure appropriate for a multi-site clinical trial and prepare the documents required for an IND. These documents include synthesis and testing SOPs, specific sections of the IND, and an IND-enabling protocol. The required precursor for trials was obtained by subcontract to a commercial supplier.

Milestone: Automated synthesis completed and SOP preparation is underway

Achievements leveraged in 2005

^{64}CuATSM (^{64}Cu-Diacetyl bis(N-4-methylthiosemicarbazone) is a PET imaging agent for hypoxia accepted into the DCIDE program. In 2005 the pre-clinical toxicology package was completed and transferred under MTA to the investigator, whose investigator-initiated IND was accepted by the FDA in September 2005. A phase I/II trial of safety and imaging feasibility and efficacy is currently recruiting patients. No *I2 Imaging* funding was required as DTP funded the development, manufacturing, and testing of a pharmaceutical grade precursor kit and the investigator funded the IND and trial.

Milestones:

- Pre-clinical package completed
- Precursor development funded by DTP
- Investigator IND accepted by FDA and Phase I/II trial underway

^{111}Indium-labeled Herceptin (trastuzumab) has been developed by NCI intramural investigators. Substantial pre-clinical work has been performed with a chelate-functionalized Herceptin using the γ-emitter ^{111}In for imaging and the α-emitter ^{213}Bi for radiotherapy. While the non-clinical work appears promising, these labeled agents have not been tested in humans. The active drug Herceptin was acquired and a contract was placed to produce a pharmaceutical grade precursor for labeling with the desired isotope. Imaging feasibility will be demonstrated in breast cancer patients with known HER-2 expressing tumors and the localization and pharmacokinetics will be evaluated in patients with peritoneal tumors expressing HER-2. The labeled drug will provide both proof-of-principle data and direct therapy development. The long-term goal of this project is to label the drug with an α-emitter for therapy. Then, imaging will become the means of patient selection and individualized therapy modeling. A significant expense will be obtaining sufficient Herceptin to perform the labeling and obtain required testing on the labeled compound to perform first in man studies. These studies were funded by I^2 *Imaging*.

Milestones:

- Herceptin acquired from Genentech
- Contract for GMP CHX-A chelated Herceptin placed ($240,000 funded by DTP)
- Phase 0 protocol developed and reviewed

Future Plans

^{18}F-Galacto-RGD is a PET agent for the imaging of the $\alpha_v\beta_3$ integrin that is expressed by endothelial cells during angiogenesis. This probe has been used in human subjects in Europe, with the initial studies showing potential for measuring angiogenesis *in vivo*. This agent has completed pre-clinical testing in DCIDE and the pre-IND data package is now being finalized. This probe does not have an IND and has been synthesized only by a complex manual three-stage technique. For this to be a useful probe beyond single site research applications, an automated and optimized synthesis will be required. I^2 *Imaging* FY2006 funds will be applied to develop an automated synthesis procedure and provide CMC and QC SOPs required for first in man studies.

Milestone: Pre-clinical safety/pharmacology/toxicology package completed

^{11}C-SN38 (**7-ethyl-10-hydroxycamptothecin**) is an active metabolite of irinotecan, a camptothecin analog and novel anti-cancer agent with anti-tumor activity in a variety of human malignancies. DHHS investigators have considerable experience with SN-38 and have a patent pending on it. Resistance to irinotecan is at least in part due to the up-regulation of the ABCG2 efflux pump, which might be reversible by modulators. Several attempts are underway by investigators to image the kinetics of efflux pumps, mainly ABCB1, with labeled therapeutic drugs such as the taxanes. The first step in this project is the development of the ^{11}C radiosynthesis to produce ^{11}C-SN38. This work will be performed at an extra-mural PET center. First-in-man studies are planned for FY2007.

Milestone: RFP for radiochemistry being developed.

^{18}F-FLT (^{18}F-fluoro-L-thymidine). FLT is a well-characterized PET probe for imaging cellular proliferation. Currently CIP is enabling multi-site production of ^{18}F-FLT at NCI's four Phase I/II imaging contract sites on an automated synthesis system provided through a CTA with General Electric Medical Systems. Expansion beyond a few contract sites to a Phase III trial does not appear feasible using this production model.

Private-sector commercial production and distribution infrastructure for the short half-life (about 2 hour) PET imaging agents exist due to the widespread clinical use of FDG. *I² Imaging* will engage the private sector by a contract to a commercial entity having the capacity for cGMP production and distribution to produce and distribute short half-life tracers for larger scale trials of FLT and as a potential provider for future probes with radionuclides of similar half-life. The strategy here is to leverage this private-sector infrastructure by providing an incentive to commercial entities to develop high-priority investigational probes that they would otherwise not be interested in because of current market and reimbursement models. The value of the existing distribution network established by these entities is substantial. *I2 Imaging* will fund the cost to initiate commercial synthesis to meet the CMC/QC specs in the NCI IND. The actual probe cost will be borne by the investigators in specific trials.

Milestones: Planned and developed timeline
Negotiation of final contract underway

Imaging Technology for Oncology

Vision: By 2015, imaging technology will play a significant role in reducing suffering and death due to cancer.

Goal: Provide publicly accessible clinical trial image databases linked to clinical outcomes as resources for the development of quantitative image tools applicable to cancer.

- **Product line leader: Larry Clarke**
- **Product line consultants:** Houston Baker, Jim Deye, Carl Jaffe, Lalitha Shankar, Barbara Croft, Keyvan Farahani, Carl Jaffe, Guoying Liu
- **Milestones achieved for 2005:**
  - First lung image cases available on web site for download
  - Public-private partnership for Image Database Research Initiative (IDRI) established and funded over 2 years
- **Milestones for 2006:** Establish another PPP for CT and PET-CT archive to permit development of change analysis tools

This product line is particularly synergistic and integrated with the Imaging Tools for Late Therapy Development and the Informatics Product Lines.

Achievements leveraged in 2005

Extension of Lung Image Database Consortium (LIDC).
The objective of this project is to develop a public database of CT images from NCI-funded and other lung cancer screening trials (e.g., NCI NLST lung trial) as a resource to develop software tools. The goals are to provide a standard means to assess software performance for oncology imaging, so that academic and industry investigators can compare performance and select the best software tools for lung cancer investigations. These computer-aided diagnosis (CAD) tools will assist in detecting and classifying abnormalities.

The LIDC consortium has accumulated over 130 cases of CT images since summer of 2005, and should meet its target accrual of 400 cases by late Sept 2006. Two publications have been submitted on the design and characterization of this database in 2005, with one accepted for publication. The image data are available from the NCI imaging web site (http://imaging.nci.nih.gov/i3/) and the research community has already used these data for presentations at two national medical imaging meetings (RSNA, SPIE). By April of 2006, this robust web searchable database will permit researchers to selectively download images and use the annotated data for the evaluation of software tools.

The Foundation of NIH in collaboration with NCI extramural staff, FDA, NIST, and LIDC formalized a PPP with eight device companies in September 2005, the Image Database Research Initiative (IDRI). The goal is to expand on the LIDC project and

archive by Sept 2007 a total of 1000 CT screening cases and 300 chest X-ray cases correlated with the CT. These images will be annotated to facilitate the evaluation of software tools. The purpose is to create a standard method to benchmark software tools for lung cancer screening and diagnosis. The steering committee (SC) of IDRI includes FDA and NIST scientists. The SC has meet on three occasions and industry has fully participated in this project. The FDA has agreed to explore whether this database resource can be a means to accelerate FDA approval of CAD tools, and NIST has agreed to explore how they can develop standard methods that can be recognized by industry on a national and international scale.

Reference Image Database to Evaluate Drug Response (RIDER). The success of the LIDC project encouraged NCI to explore a second PPP to support the creation of a CT and PET-CT database of lung cancer cases (as opposed to screening cases) to evaluate change analysis software tools for quantitatively measuring tumor response. Change analysis tools are important as physicians have significant inter- and intra-observer variability in the visual assessment of tumor response. Software tools to determine total tumor volume or standard uptake values (SUV) for PET-CT have not yet been benchmarked in a standardized way against a reference database. This resource would permit open competition for assessment of different change analysis tools and if successful and implemented in therapeutic clinical trials could decrease the number of subjects required to achieve statistical power. For the RIDER project, the five institutions in the LIDC group were expanded to include the MD Anderson and Memorial Sloan Kettering Cancer Centers. With partial funding from *I² Imaging*, over 100 serial cases have been accrued and posted on the NCI web site. The FNIH is now engaged in discussion with the device and drug industry to create a second PPP for the RIDER image database, which will provide leverage to the *I² Imaging* support.

Future Plans

We will continue to develop web-accessible resources for the development and evaluation of image data collection and analysis methods, with a specific emphasis on quantitative measurement of response to therapy, in accordance with the OBQI and IOTF initiatives. Plans include the following:

- Accelerate data collection and annotation for the RIDER database in FY 06 and FY 07 to include additional serial CT and PET-CT data for lung cancer
- Demonstrate that RIDER can be used to evaluate change analysis methods for response to therapy.
- Expand this database to include other imaging systems and organ systems, for example, DCE-MRI for assessment of brain tumor response. The image and metadata will be collected from retrospective and prospective clinical trials supported by *I² Imaging*, ACRIN, CTEP, and the pharmaceutical industry.
- Expand collaborations with NIBIB and the FDA, consistent with the IOTF. NIBIB will support research fellows at the FDA and NIST to develop improved statistical methods for measurement of change analysis for response to therapy.

- Expand the collaboration with NIST, through a workshop planned for Sept 14-15th 2006, "Imaging as a Biomarker: Standards for Change Measurement in Therapy". The goal of this workshop is to define international standards for imaging hardware and software tools for the measurement of response to therapy

Imaging Informatics (I^2I^2) Product Line

Vision: By 2015, the NCI imaging informatics infrastructure will be an indispensable resource for oncology research and clinical care.

Goal: Create an informatics infrastructure so pervasive and useful that its existence will be taken for granted by those who use it.

- **Product line leader: Eliot Siegel**
- **Product line consultants:** Larry Clarke, Gary Dorfman, John Freymann, Carl Jaffe, John Perry
- **Milestones achieved for 2005:**
  - Creation of National Cancer Imaging Archive (NCIA) and archival support storage and retrieval of images,
  - Initiation of the In vivo Imaging Workspace in caBIG
  - Engaged Dr. Eliot Siegel as an IPA
- **Milestones for 2006:**
  - Extension of NCIA features: security, annotation, curation, searching, additional databases
  - Projects funded by caBIG Imaging Workspace
    - Vocabulary: incorporation of ACRIN, RadLex and DICOM into caDSR
    - Software: eXtensible Imaging Platform (XIP) for image review and algorithm testing and development, and collaboration
    - Standards and Interoperability: standard for mark-ups and annotation
    - Testbed demonstrations

The strategy to achieve the goal of the *I2 Imaging* Informatics Product Line is to provide fundamental infrastructure to integrate and support the secure transmission, archiving and analysis of research imaging data and metadata, to implement and extend the caBIG in vivo Imaging Workspace and National Cancer Imaging Archive (NCIA), and to implement the associated operational support framework to promote their use and expansion. This product line is particularly synergistic and integrated with the Imaging Tools for Late Therapy Development and the Imaging Technology for Oncology Product Lines.

Achievements funded in 2005

NCIA: http://ncia.nci.nih.gov

- Creation of a structure for the product line, a technical committee and a combined users and steering committee
- Recruited Dr. Eliot Siegel as imaging champion, April 2005
- Continuing development of NCI MIRC (Medical Imaging Resource Center) clinical trials software with RSNA (Radiological Society of North America)

- Meeting of experts to create mapping from DICOM elements to Enterprise Vocabulary Services/Common Data Elements (EVS/CDE) and caDSR (cancer Data Standards Repository)
- Creation of National Cancer Imaging Archive – NCIA, with a current capacity of approximately 10 Terabytes with full backup services nightly
- Archival Support for LIDC, RIDER, IDRI: storage and retrieval of image sets

caBIG In vivo Imaging Workspace

https://cabig.nci.nih.gov/workspaces/Imaging/

- 15 SMEs (Subject Matter Experts) named in late summer 2005
- First teleconference in Fall 2005 and the first face-to-face in mid-December 2005 in Philadelphia
- 4 special interest groups (SIGs) formed
  - Software
  - V/CDE (Vocabulary and Common Data Elements)
  - Standards and Interoperability
  - Testbed

Future Plans

NCIA: Extension of features of NCIA

- Security functionality to allow limited access when appropriate for ongoing studies or those not released to the public,
- Support for image annotation and mark-ups
- Support for image curation
- Additional download features such as user subscription to pre-defined search criteria
- Additional databases such as the virtual colonoscopy database from DoD and ACRIN

caBIG: In vivo Imaging

- Vocabulary
  - Incorporation of ACRIN terms into caDSR
  - RadLex "Playbook" (standardized terminology for imaging devices, diagnostic studies, procedures, sequences)
  - Incorporation of DICOM tags into caDSR
- Software
  - Creation of eXtensible Imaging Platform (XIP) for image review and algorithm testing and development, and collaboration
  - Standards and Interoperability
  - Development/adoption of "standard" for mark-ups and annotation
- Testbed
  - Creation of "middleware" between DICOM/HL7 and caGRID
  - Major RSNA and other venue demonstration of caBIG Imaging Workspace projects including use of GRID for images from clinical trials

Summary of Progress Toward Company-level Goals

- Qualify imaging tests as biomarkers for therapy development
  - Two trials planned for 2006 with FDG-PET
  - Trial planned for 2006 with DCE-MRI
  - Trial planned for 2006 with FLT-PET
  - UPICT initiative to standardize techniques
  - IRATs funded
- Support development and delivery of image-guided interventions
  - Workshop held to plan program
  - FDG-PET added to 2006 RFA trial
- Make new imaging agents and technology available for research and clinical use
  - Pre-clinical studies completed on two agents
  - Synthesis initiated on four agents
- Improve imaging informatics infrastructure
  - NCIA established with RIDER, LIDC, and IDRI as the first databases
  - *In vivo* Imaging Workspace established
  - Archive workshop planned for 2006
- Advance the role of imaging to detect and treat preneoplastic lesions
  - Workshop planned for 2006
- Improve our understanding of communications between cancer cells and their environment
  - Workshop planned for 2006
  - Cancer imaging camp planned for 2007

Glossary of Acronyms

ACOSOG	American College of Surgeons Oncology Group
ACR	American College of Radiology
ACRIN	American College Of Radiology Imaging Network
ATC	Advanced Technology Consortium
caBIG	Cancer Bioinformatics Grid
caDSR	cancer Data Standards Repository
CALGB	Cancer and Leukemia Group B
CCB	Cancer Centers Branch
CCOP	Community Clinical Oncology Program
CCR	Center for Cancer Research
CIP	Cancer Imaging Program
CMS	Centers for Medicare & Medicaid Services
COG	Children's Oncology Group
CRADA	Cooperative Research and Development Agreement
CT	Computed tomography
CTA	Clinical Trial Agreement
CTEP	Cancer Therapy Evaluation Program
CTSU	Clinical Trials Support Unit
CTWG	Clinical Trials Working Group
DCB	Division of Cancer Biology
DCCPS	Division of Cancer Control and Population Sciences
DCE-MRI	Dynamic contrast enhanced MRI
DCEG	Division of Cancer Epidemiology and Genetics
DCP	Division of Cancer Prevention
DCTD	Division of Cancer Treatment and Diagnosis
DEA	Division of Extramural Activities
DFS	Disease-free survival
DICOM	Digital Imaging and Communications in Medicine
DTP	Developmental Therapeutics Program
EVS/CDE	Enterprise Vocabulary Services/Common Data Elements
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FDHT	Fluorodihydrotestosterone
FES	Fluoroestradiol
FLT	Fluoro-L- thymidine
FMISO	Fluoromisonidazole
HL7	Health Level 7 (standards electronic healthcare information)
IDRI	Image Database Research Initiative
IGI	Image-guided Intervention
IOTF	Interagency Oncology Task Force
IPA	Intergovernmental Personnel Act
IRAT	Image Response Assessment Teams
LIDC	Lung Image Database Consortium

LOI	Letter of Intent
MR/MRI	Magnetic resonance/magnetic resonance imaging
NCIA	National Cancer Image Archive
NIST	National Institute Of Standards And Technology
NLST	National Lung Screening Trial
NTROI	Network Translational Research for Optical Imaging
NSCLC	Non-small cell lung cancer
OBQI	Oncology Biomarker Qualification Initiative
OS	Overall survival
OSPA	Office of Science Planning and Assessment
OTIR	Office of Technology and Industrial Relations
PBTC	Pediatric brain tumor consortium
PET	Positron emission tomography
PFS	Progression-free survival
PPP	Public Private Partnership
PRC	Protocol Review Committee
QARC	Quality Assurance Review Center
RADLEX	Radiology Lexicon (for uniform indexing and retrieval of radiology information)
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	Radiofrequency Ablation
RIDER	Reference Image Database To Evaluate Response
RSNA	Radiological Society Of North America
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
SME	Subject Matter Expert
SOW	Statement of work
SPECT	Single Photon Emission Computed Tomography
SUV	Standard Uptake Value
SWOG	Southwest Oncology Group
UPICT	Uniform Protocols For Imaging In Clinical Trials
V/CDE	Vocabulary/ Common Data Elements

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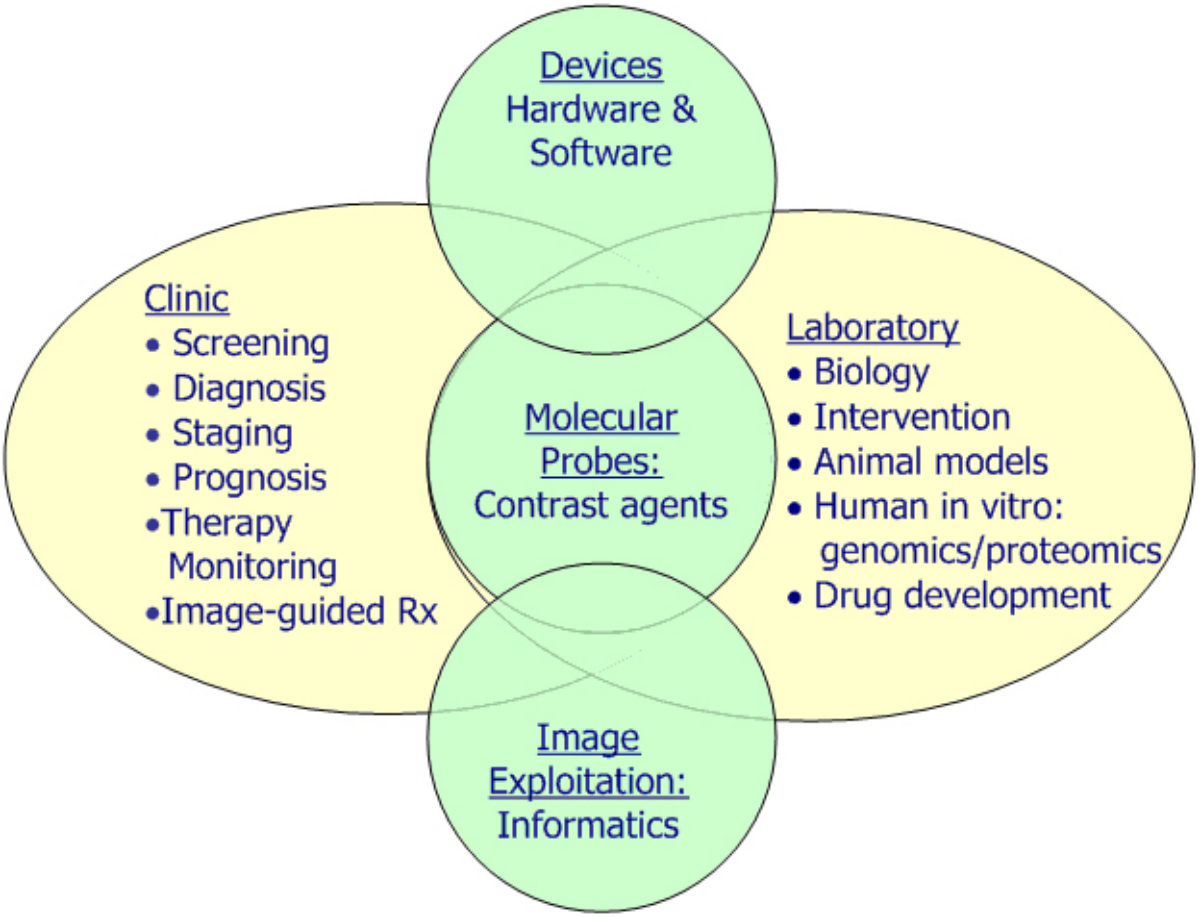

June 2006